Ichthyosis Follicularis with Atrichia and Photophobia Syndrome: First Case Report in Thailand

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ABSTRACT

We herein describe the first reported case of Ichthyosis Follicularis with Atrichia and Photophobia (IFAP) syndrome in Thailand. A 6-year-old boy presented with a history of photophobia since 1 month of age. Then he developed widespread follicular hyperkeratotic papules and subtotal non-scarring alopecia by the age of 10 months and 5 years, respectively. Sparse eyelashes and nail dystrophy were also noted. No neurological abnormalities, systemic involvement, and hearing impairment were observed. The clinical manifestations were consistent with IFAP syndrome, although genetic testing did not confirm the diagnosis of this rare disorder.

Keywords: IFAP syndrome; *MBTPS2* (Siriraj Med J 2017;69: 156-158)

INTRODUCTION

Ichthyosis Follicularis with Atrichia and Photophobia (IFAP) syndrome is a rare X-linked disorder characterized by the triad of ichthyosis follicularis, alopecia and photophobia. Recently, the mutation of the gene *MBTPS2* (membrane-bound transcription factor protease site 2) has been identified to be the causation of this condition. Until now, less than 50 cases have been reported. This report describes the clinical manifestations of a case of IFAP syndrome and reviews the literature.

CASE REPORT

The patient was a product of nonconsanguineous marriage. He was born at term after an uneventful pregnancy. By 1 month of age, the mother noticed that her baby developed intense photophobia with redness and watering of both eyes. The epithelial defect at the central cornea and diffuse neovascularization was noted by ophthalmologist. Herpes keratitis was diagnosed and was treated by systemic acyclovir for 6 months, even though the polymerase chain reaction and viral isolation from corneal scraping were all negative. Regular lubricant eye drops were also prescribed. Diffuse corneal neovascularization was still seen, but the symptom of photophobia was improved. He could open his eyes widely in normal light Fig 1.



Fig 1. Diffuse non-scarring alopecia with sparse hair and photophobia.

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Received 31 March 2016 Revised 1 July 2016 Accepted 26 September 2016
doi:10.14456/smj.2017.31

He had roughness of skin over the arms and legs since 10 months of age. Nail changes were observed at that time. By the age of 5 years, he developed generalized hair loss involving scalp hair and eyelashes. The teeth were normal. He had normal developmental milestone. There was no family history of similar conditions.

On examination at age 6, his weight, height and head circumference were 16 kg (10^{th} - 25^{th} centile), 106 cm (10^{th} - 25^{th} centile) and 52 cm (50^{th} - 75^{th} centile). Dermatologic examination revealed widespread non-inflammatory spiny perifollicular papules and psoriasiform-like plaques that were prominent on extensor surface of the elbows and knees Fig 2. He notably had diffuse sparse and brittle hairs. His eyelashes were present but diminutive. Nail dystrophy on the middle finger of the left hand and on the toes was seen. He was otherwise healthy.

Investigations including complete blood count, liver function test, renal function test, and vitamin A level were all normal. Audiogram, development and intelligence were normal by formal assessment. Histopathologic findings from the elbow revealed focal hyperkeratosis columns and compact orthokeratosis of the epidermis Fig 3.



Fig 2. Cutaneous "thorn-like" projection over the extensor aspect of the extremities.

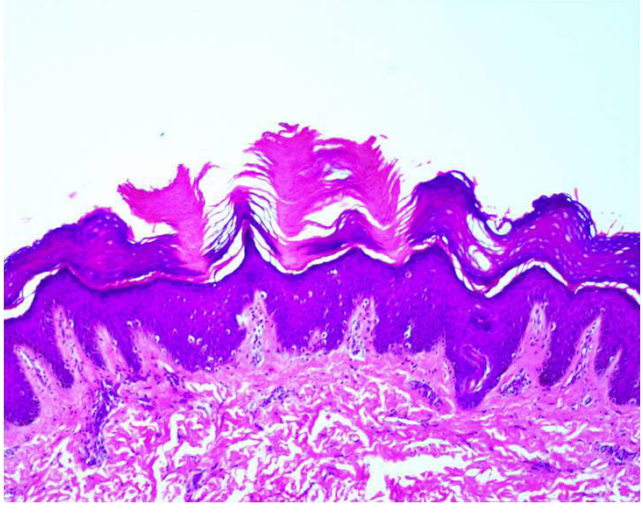


Fig 3. Slight acanthosis with focal parakeratotic columns of epidermis.

A clinical diagnosis of IFAP syndrome was made. Genomic DNA was extracted from white blood cells using standard methods. PCR amplification was performed on all 11 exons and intron/exon boundaries of the *MBTPS2* gene using laboratory designed primers and IMMOLASE™ DNA polymerase (Bioline). The PCR products were sequenced using The BigDye® Terminator v3.1 Cycle Sequencing kit and then analyzed on an automated DNA sequencer (Applied Biosystems). In addition, total RNA was extracted from lymphocytes and full-length complementary DNA (cDNA) was synthesized using SuperScript® III First-Strand Synthesis System for RT-PCR kit (Invitrogen). The entire coding sequence of *MBTPS2* transcript was amplified. However, no pathogenic *MBTPS2* mutation was identified in both genomic DNA and cDNA level in this patient.

DISCUSSION

IFAP syndrome (MIM # 308205) is a distinctive X-linked oculocutaneous genetic disorder. It was first described by MacLeod in 1909.[1] Characteristic findings of this rare syndrome comprise ichthyosis follicularis, subtotal to total alopecia, and photophobia.[1-3] Atrichia or hypotrichosis is the most prominent finding of the syndrome.[3] It usually presents at birth, but occasionally it may be noted later in life. The classic cutaneous feature is widespread non-inflammatory follicular papules, "thorn-like" projections, predominantly distributed on the scalp and extensor surface of the extremities. Other cutaneous findings including generalized xerosis, psoriasiform plaque, nail dystrophy, angular stomatitis, and palmoplantar keratoderma were also reported.[3,4] The histopathology of the skin is rather non-specific.

The third constant feature is photophobia of varying degree. It may exist since birth or may develop later.[5] It possibly results from vascularizing keratitis or anomalies in Bowman's membrane together with epithelial adhesion defects.[6] The other ocular findings are corneal scar, punctuate keratopathy, corneal neovascularization, cataract, and nystagmus.[6] Non-constant systemic findings reported in the literature include failure to thrive, renal and vertebral anomalies, recurrent respiratory and skin infections, and neurological abnormalities such as developmental delay, epilepsy, progressive cognitive decline, and cerebral atrophy.[2,4,5,7]

MBTPS2 is an intramembrane zinc metalloprotease

essential for cholesterol homeostasis and endoplasmic reticulum stress response. Mutation in *MBTPS2* gene was found to be the cause of the disease by Oeffner et al.[3] Until now, twenty-one missense mutations and intronic mutations partially affecting transcription have been described.[8-10] More severe mutations for example, nonsense, out-of-frame mutations, or deletion/duplication may cause nonviable phenotype. The mutation of this gene results in functional deficiency of *MBTPS2*, and the level of residual activity correlates with the clinical severity of the patient.[3,8,9] In line with X-linked mode of inheritance, affected men suffer from the full-blown clinical phenotype, whereas female carriers may present with mosaic pattern of minor symptoms such as follicular ichthyosis, alopecia and hypohidrosis following the line of Blaschko.[11] In this patient, the clinical manifestations were compatible with IFAP syndrome. However, no pathogenic *MBTPS2* mutation was identified in the genomic DNA of this patient.

So far, *MBTPS2* gene is the only known causative gene of IFAP syndrome. From the largest series reporting *MBTPS2* mutations, all 13 families with IFAP syndrome were identified with *MBTPS2* mutations.[9] There has been no study regarding the genetic heterogeneity of IFAP syndrome or detectable rate of the standard PCR and sequencing of *MBTPS2* gene with genomic or cDNA. An unidentified mutation in this patient could be due to many possibilities: for example, a mutation is located in unexplored regions, such as regulatory element, promoter, or intronic regions rendering it undetectable by our methods; or this patient could have the diseases resembling IFAP syndrome. Differential diagnosis includes keratitis, ichthyosis, and deafness (KID) syndrome and keratosis follicularis spinulosa decalvans (KFSD). KID syndrome shares many features with IFAP such as keratitis, hyperkeratotic skin lesions, nail dystrophy and alopecia. However, hearing loss is an essential finding in KID syndrome which was not found in this patient. KFSD is a rare X-linked recessive disorder characterized by widespread follicular hyperkeratosis, scarring alopecia of the scalp, eyebrows and eyelashes, photophobia and corneal dystrophy. It results from mutations in the *MBTPS2* gene the same as IFAP which emphasizes the clinical spectrum and overlapping molecular pathology of these two disorders. KFSD differs from IFAP in that there is presence of progressive cicatricial alopecia, unlike the true congenital atrichia seen in IFAP syndrome.

The prognosis of IFAP syndrome depends on associated systemic manifestations. The cutaneous lesions may improve with emollient, topical corticosteroid, and tretinoin. Acitretin has been used in some patients.[12, 13] It led to improvement in the fluorescein pattern of ocular involvement and follicular keratinization. However, photophobia, corneal neovascularization and alopecia remained unchanged. Symptomatic therapy including emollient to alleviate roughness of skin, topical minoxidil and chelated zinc for alopecia, and lubricant eye drops for ophthalmologic conditions were prescribed in this patient. His overall condition got better. He had less photophobia and could do normal daily activities. Even though he had subnormal visual acuity, he could attend the regular school with low visual aid.

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